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Opsoclonus/Myoclonus: Paraneoplastic Syndrome of Neuroblastoma

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Anna Janss, MD, PhD (Pediatric Neurooncologist)

The two children under discussion today had an unusual though well-recognized presentation of neuroblastoma. Review of their clinical course, outcome, and the literature on this syndrome may help in the management of similar patients.

Our first patient is a 4-year-old right-handed male who was well until age 29 months. He developed normally until 1 week prior to presentation when he developed upper respiratory symptoms and facial flushing. No fevers, weight loss, or bruising were reported. One day prior to admission, he became very clumsy, unable to sit up or walk independently. Physical examination on admission was remarkable for severe truncal and appendicular ataxia, without mention of unusual eye movements. The remainder of his examination was normal. His evaluation is summarized in Table I.

A radical nephrectomy with gross total resection of the tumor was performed. The pathologic diagnosis was that of a well-differentiated neuroblastoma. The copies of N-*myc* were less than 10. Due to his favorable diagnosis, stage II neuroblastoma, and complete resection he was discharged without requiring further treatment. His neurological examination at that time was remarkable for mild ataxia and hyporeflexia.

He developed otitis media 3 months later and subsequently an unsteady gait. Neurologic examination at that time revealed irritability, dysarthria, poor expressive speech, intermittent opsoclonus, severe dysmetria, and truncal ataxia with retropulsion. CT scans of the chest and abdomen showed no evidence of tumor; MRI of the brain and examination of the spinal fluid were normal. All laboratory tests including serum HVA and VMA, and ferritin were normal. The ataxia improved after treatment with antibiotics.

There were three episodes of opsoclonus and recurrent ataxia in the next 8 months each preceded by otitis media, and one preceded by surgical correction of a left esotropia. The first three resolved partially after treatment with antibiotics and the most recent after a 3 month course of prednisone (100 mg p.o. daily).

The boy is now almost 5 years old. His examination is remarkable for a clinging, irritable personality with dysarthria, aphasia, and motor and cognitive developmental delay. His left esotropia persists. He has mild dysmetria (right greater than left), and a wide-based gait with retropulsion. The remaining neurologic examination is normal. He is unable to attend school and is currently being evaluated for special education.

The second patient is a 4-year-old girl who was well until age 21 months when she developed hyperemesis. A gastroenterologic work-up was unrevealing. She then became unable to walk. A neurological examination upon admission here revealed a severe appendicular and truncal ataxia and "dancing eye movements." The remainder of her evaluation is outlined in Table I. She underwent resection of a $2 \times 1 \times 1$ cm mass in the celiac axis along with two enlarged lymph nodes. All specimens showed neuroblastoma with low N-*myc* copy number and favorable histology.

Her postoperative recovery was uneventful. However, she was discharged from the hospital without change in her neurological symptoms: dysarthria and delayed language skills, opsoclonus, truncal ataxia and titubation, bilateral dysmetria, generalized myoclonus, and inability to walk. A trial of propranolol was not efficacious. She then was treated with prednisone (50 mg daily for 3 months) with partial improvement in her neurological

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TABLE I. Initial Evaluation of the Two Index Patients*

Study	Pt #1	Pt #2
CT of the brain	Normal	Normal
Spinal fluid	Normal, 1 WBC; 10 RBC; protein 12/glucose 67; cultures negative	Normal, 2 WBC; 172 RBC; protein 14/glucose 55 cultures negative
CBC	Normal except for Hb = 10	Normal
Spot VMA	Positive	Negative
24 hr VMA	Elevated	Not available
Ferritin	24	28
Chest X-ray film	Normal	Normal
Abdominal X-ray film	Calcification in left retroperitoneal area	Normal
Abdominal CT	5 × 6 × 7 cm extra-adrenal mass above the left kidney[a]	Small celiac axis mass[a]
Bone scan	Negative	Negative
Bone marrow biopsy	Negative	Negative
Lyme disease	Negative	Negative
ESR	Not available	3
RPR	Not available	Negative
RF	Not available	Negative
ANA	Not available	Negative

*WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin in mg/dl; cm, centimeter; CT, computerized tomography; ESR, erythrocyte sedimentation rate; RPR, serology for syphilis; RF, rheumatoid factor; ANA, antinuclear antigen.
[a]Shown in Figures 1 and 2, and discussed by Dr. Jeffrey Johnson.

symptoms. Treatment with high dose intravenous γ-globulin yielded further improvements.

She is now 4 years old. Her current examination is remarkable for mild truncal instability and delay in expressive language skills. She has had three recurrences of ataxia associated with viral illnesses. Neuropsychiatric testing indicated normal receptive and cognitive abilities. There has been no evidence of recurrent neuroblastoma radiographically.

Dr. Johnson, would you please review the pertinent radiological findings in these two cases?

Jeffrey Johnson, MD (Radiology Fellow)

Radiologic evaluation of both patients included contrast-enhanced CT examination of the chest, abdomen, and pelvis, bone scintigraphy, and gadolinium-enhanced MRI of the brain. Studies were completed within a 5-day period in each patient.

Abdominal CT study of the first child shows a large mass (large arrows) that is compressing and possibly invading the left kidney (Fig. 1). The mass enhances heterogeneously and contains punctate calcifications anteriorly. Compression of the left renal collecting system is producing mild hydronephrosis (small arrows). Periaortic adenopathy (n) is also present. Other images demonstrate encasement of the left renal vein (rv). The left adrenal gland is only partially visualized, with tumor involvement of the lateral limb (not shown). The chest CT, bone scan, and MRI of the brain showed no evidence of metastatic disease.

The abdominal CT (Fig. 2) of the second patient demonstrates a 1.5 cm lobulated mass of low attenuation (arrows) located in the portacaval space. The adrenal glands appear normal. The mass was the only imaging manifestation of neuroblastoma in this patient. The remainder of the radiologic workup was negative.

Dr. Janss. Were there any striking findings on microscopy, Dr. Chatten?

Jane Chatten, MD (Pediatric Pathologist)

The histopathology of both patients was similar. They both have the characteristics of so-called "favorable histology" neuroblastoma according to the Shimada criteria [1] (Fig. 3). They are stroma-poor befitting their young age, exhibit differentiation toward ganglion cells, and are favorable because their mitotis-karyorrhexis indices are low, with virtually no mitotic activity. Review of the 4 other opsoclonus patients in our files (among about 400 neuroblastoma cases) shows the same histologic pattern.

Dr. Janss. Was there evidence of a prominent inflammatory infiltrate? This feature has been emphasized by some of the authors reporting cases such as these.

Dr. Chatten. There is no unusual infiltrate. There are often lymphoid follicles visible in maturing neuroblastomas, sometimes enough to suggest they are involved lymph nodes, but this is not peculiar to opsoclonus pa-

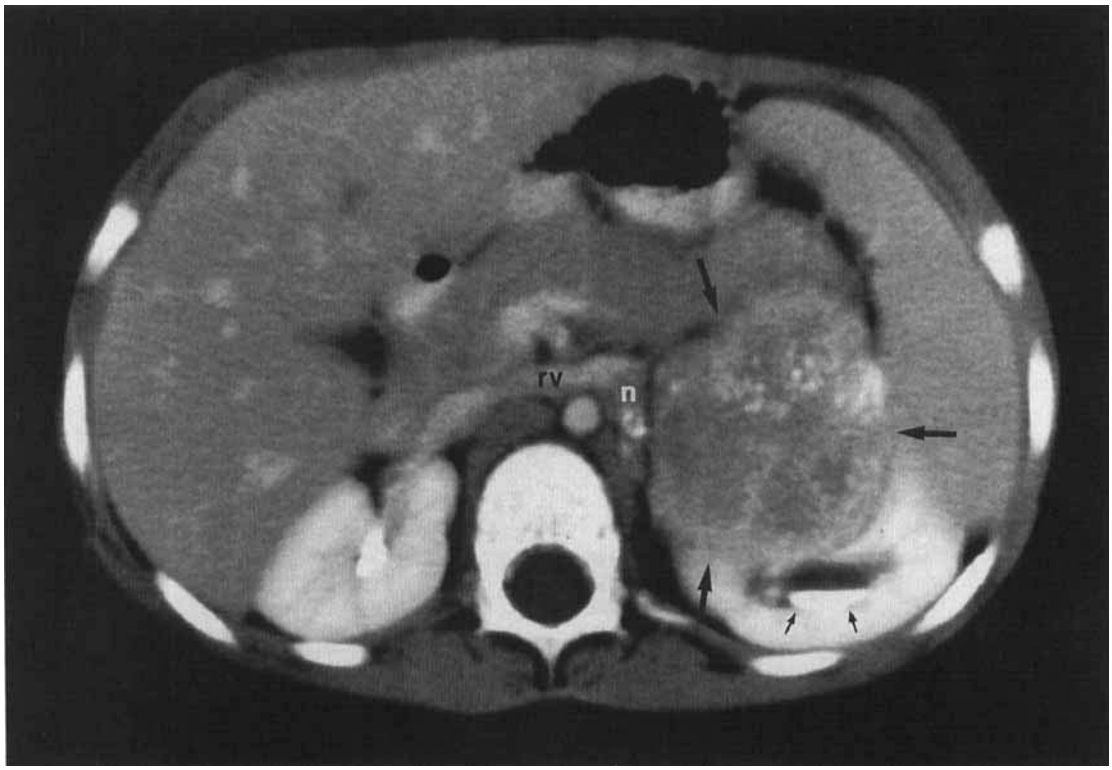

Fig. 1. Abdominal CT. A large mass (large arrows) compresses the kidney and possibly invades that organ. Abbreviations explained in text.

tients. If I had to select a histologic feature seen in their tumors, it would be the presence of fairly advanced maturation, perhaps enabling the cells to generate a substance or antigen that produces or permits opsoclonus.

G.J. D'Angio, MD (Pediatric Radiation Oncologist)

Dr. Janss, I note that you say that close follow-up of both patients reveals no evidence of residual disease in either one. In view of the persisting signs in patient number 2, however, I wonder how assiduous the search has been for a possible small tumor nidus?

Dr. Janss. There has been a meticulous search, and there is absolutely no evidence of tumor anywhere either on imaging studies or on the basis of any of the markers such as catecholamines.

These children illustrate the syndrome of *myoclonic encephalopathy of infancy* first described by Kinsbourne in 1962. It is therefore also called Kinsbourne's syndrome. Other terms are the syndrome of dancing eyes and dancing feet, acute cerebellar encephalopathy, or the syndrome of opsoclonus-myoclonus [2,3]. The association with neural crest tumors such as neuroblastoma or ganglioglioma was made 6 years after Kinsbourne's report by Solomon and Chutorian [4]. It is thus a paraneoplastic syndrome; that is, a rare, idiopathic clinical picture associated with the presence or eventual appearance of a neoplasm. It is estimated that approximately 2% of children with neuroblastoma present with acute cerebellar encephalopathy, and their mean age at presentation is 18 months (range 8 months–5 years) [5]. Opsoclonus/myoclonus has also been reported in adults with somatic neoplasms including breast, ovarian, and thyroid carcinoma [6] but this discussion will be limited to the pediatric population and those cases associated with neural crest tumors.

The syndrome in children is characterized by the acute or subacute onset of any combination of the symptoms shown in Table II. The ataxia seen in these children may be either truncal, appendicular, or both. Myoclonus is a rapid involuntary muscle jerk of central origin, while opsoclonus is the involuntary, fluttering, multidirectional darting of the eyes [3,7]. The cognitive dysfunction including diminished language and attention skills is often overlooked due to the dramatic impairments of balance and muscle control. Patients may exhibit dysconjugate gaze, but the remainder of the cranial nerve examination should be normal. Although strength and sensation are intact, muscle tone is often diminished. Deep tendon reflexes may be normal to diminished and plantar responses, normal or extensor.

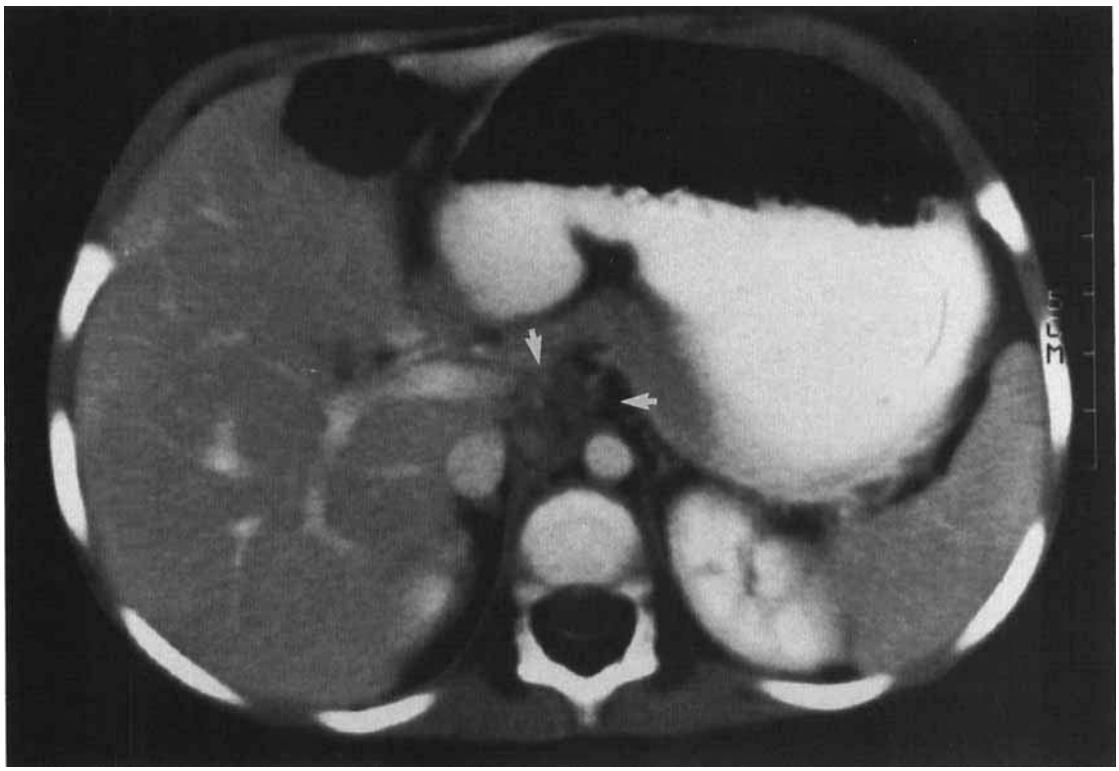

Fig. 2. Abdominal CT. The arrows point to a small mass in the portacaval space.

Dr. D'Angio. You say the syndrome can be seen with other disease states in adults; is it, however, manifest exclusively with neuroblastomas during the childhood years?

Garrett Brodeur, MD, PhD (Pediatric Oncologist)

That is generally true, but it should be noted that it can occur in children without there being an identifiable tumor at diagnosis.

Beverly Lange, MD (Pediatric Oncologist)

The signs and symptoms you describe cannot be explained in their entirety by a cerebellar lesion. The cognitive problems described, for example, point elsewhere in the brain.

Dr. Janss. I agree; and the difficulty seems to be more global in character. Adults, for example, can develop coma but this has not been seen in children. Dr. Sladky, in your experience as the Director of the Neuromuscular Clinic, how do you see the problem?

John T. Sladky, MD (Pediatric Neurologist)

I agree that the difficulty seems to be more global. There is, however, recent literature implicating cerebellar dysfunction in some of the cognitive problems that appear to stem from higher levels. Insofar as the opsoclonus is concerned, it clearly is a brainstem disorder.

Dr. D'Angio. Are the extraocular movements always conjugate? I seem to recall one child where the motions were dysconjugate.

Dr. Sladky. The answer is probably, "Yes" in the sense that the eyes move in the same general direction although they may differ in the precise angles of deviation.

Dr. Lange. What about vision; do the children appear to see well enough to function?

Dr. Janss. The surprising answer is, "Yes".

Table III lists the differential diagnosis for children presenting with symptoms of opsoclonus and myoclonus [3,8].

The laboratory features of the syndrome are well illustrated by the cases presented. Hematologic, electrolyte, and hepatic enzyme profiles are all normal, as are studies for rheumatalogic disorders. Urine and/or serum catacholamines may or may not be elevated, and it is not unusual for the cerebrospinal fluid to show a mononuclear pleocytosis with increased protein and immunoglobulins [8].

Radiologic studies including chest and abdominal X-ray films may demonstrate calcified masses, but the most reliable way of demonstrating tumor remains chest or abdominal CT or MRI. Imaging studies of the neural axis and electroencephalograms are generally normal. Not all tumors are detectable using the available diagnostic technology. Approximately 60% will become evident

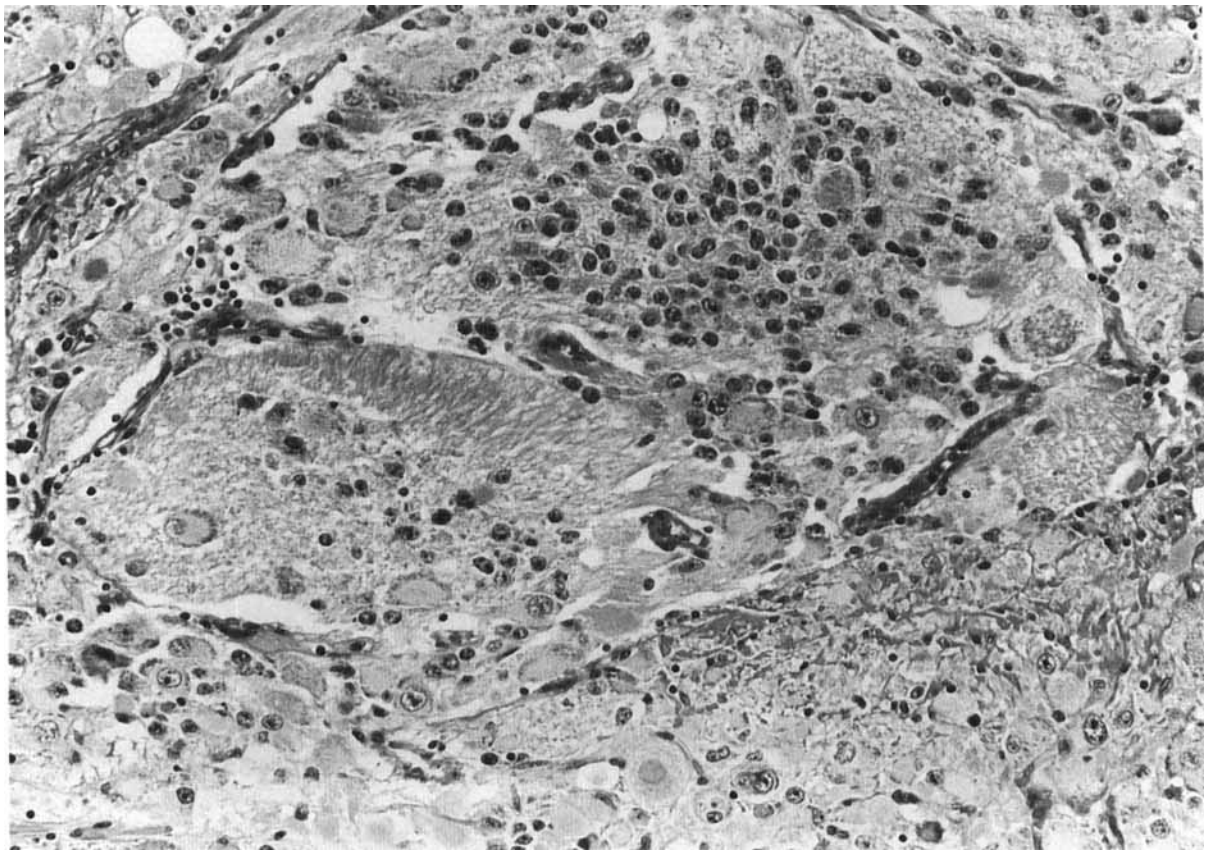

Fig. 3. Histology shows cytologic differentiation with mature ganglion cells (lower), immature neuroblasts (upper), and copious fibrillary neuropil. There is no Schwannomian stroma, mitotic activity, or karyorrhexis. Hence this tumor is a stroma-poor, differentiating, low MKI tumor—a subtype of neuroblastoma that is favorable so long as the patient is less than 5 years old.

TABLE II. Myoclonic Encephalopathy of Infancy: Presenting Symptoms

Ataxia
Myoclonus
Opsoclonus
Irritability and anxiety
Loss of expressive language
Impaired cognition
Seizures[a]

[a]Seizures associated with this syndrome have been reported in only one case (Telander et al. [9]).

within 3 months from the onset of myoclonus according to Pranzatelli [8].

Pathologic examination of the tumors shows they are generally well-localized, well-differentiated neuroblastoma or ganglioneuroblastoma, as described by Dr. Chatten. Not seen in our patients, but reported as not uncommon by others, are robust inflammatory infiltrates in these tumors, often making it difficult to distinguish tumor from adjacent lymph node [9].

Since ataxia, opsoclonus, and myoclonus are associated with an underlying neural crest neoplasm, tumor removal or other effective treatment might be expected to ameliorate those signs. However, as the cases presented illustrate, tumor cure does not assure return of normal neurologic function. Most patients described in the literature with paraneoplastic opsoclonus/myoclonus failed to improve after tumor resection [3,9] but relief of neurologic symptoms followed treatment with prednisone or ACTH. Anecdotal approaches to pharmacologic treatments of the ataxia and myoclonus include immunosuppression (corticosteroids, ACTH, plasmapheresis, intravenous immunoglobulins), antispasmodics (propranolol, clonazepam, baclofen, antihistamines), anticonvulsants, anticancer agents (cyclophosphamide, vincristine), and vitamin therapy [8]. The standard treatment in this institution for paraneoplastic opsoclonus/myoclonus at the time of presentation is prednisone, 5 mg/kg p.o. for 2 months followed by a gradual taper over 2 to 3 weeks. Histamine 2 receptor antagonists are recommended during the period of treatment to avoid gastritis.

The differential diagnosis includes EBV or Coxsackie virus encephalitis, toxic reactions notably to dilantin, and

TABLE III. Opsoclonus/Myoclonus: Differential Diagnosis

Encephalitis[a]	Coxsackie B	Epstein–Barr
	H. influenza	H. zoster
	Mumps	Lymphocytic choriomeningitis
	Neurosyphilis	Psittacosis
	Salmonella typhi	Tuberculous meningitis
	Immunization	Polioencephalitis
	Psittacosis	Rubella
	St Louis encephalitis	
Paraneoplastic syndrome associated with neural crest tumors		
Demyelinating syndromes		
Intoxications	Phenytoin	
	Amitryptyline	
	Insecticides (chlordecone or Kepone)	
	Hyperosmolar nonketotic diabetic coma	
Ideopathic		

[a]References found in Pranzatelli [8].

demyelinating processes. Finally, opsoclonys/myoclonus can be "idiopathic" but there must always be a search for an underlying neuroblastoma.

Dr. Sladky. It is of some interest that the ACTH fragments $ACTH_{4-9}$ and $ACTH_{4-10}$, which are potent anticonvulsants, are not effective in treating this syndrome. The whole ACTH molecule, however, and fragments $ACTH_{1-24}$ and $ACTH_{1-39}$, which share glucocorticoid and immunosuppressant activities, are useful therapeutic agents.

Dr. Janss. The etiopathogenesis of this paraneoplastic syndrome remains unclear. Paraneoplastic syndromes in adults have been linked to the presence of autoantibodies that target tumor antigens and cerebellar antigens (anti-Yo, anti-Hu), but no autoantibody has been consistently identified in the opsoclonus/myoclonus coincident with pediatric neural crest tumors. An autoimmune etiology is nonetheless suggested by the response of symptoms to immunosuppressive agents, and the fact that recurrence of cerebellar encephalopathy without tumor recurrence occurs only with stressors such as infection that activate the immune system.

Dr. Sladky. Another hypothesis that has no proof is that the presence of the tumor in some way excites neurotransmitter pathways [7,8].

Nancy Bunin, MD (Pediatric Oncologist)

Has anyone tried cyclosporin?

Dr. Janss. I don't believe so, although there may be some hesitancy because of the leukemias and lymphomas that have been reported in patients receiving that agent.

Children presenting with paraneoplastic opsoclonus/myoclonus have an excellent prognosis for cure of the underlying tumor. In 28 cases reviewed by Altman and Baehner [5], 2-year relapse-free survival was 89.3% which far exceeds the 2-year overall survival of 30–34% reported for neuroblastoma at that time. This difference in survival could not be attributed solely to age at presentation or the stage of the tumor, which are well described predictive factors for outcome in neuroblastoma [10]. No comprehensive study regarding other predictors of tumor outcome such as serum ferritin or tumor histology in these children is available. Therapy other than excision of tumor is rarely required for children presenting with acute cerebellar encephalopathy and neuroblastoma [9] although in earlier series, radiotherapy and chemotherapy were frequently prescribed [5].

The likelihood of long-term survival in this subgroup of neuroblastoma patients makes the prognosis for recovery of normal neurologic function crucial. Telander et al. studied the outcome of 10 children with acute cerebellar encephalopathy and neuroblastoma [9]. They found that 9 had at least one postoperative episode of recurrent cerebellar encephalopathy despite absence of obvious tumor recurrence. In all cases, the exacerbation of ataxia and myoclonus was preceded by gastroenteritis or upper respiratory infection. The mean number of recurrences per patient was 2.4 (range 0–9) and the mean postoperative interval between recurrent episodes was 14 months (range 1–36 months). Median follow-up time in this study was 7.25 years (range 1–18 years). Prednisone or ACTH was used to ameliorate the symptoms of these recurrent episodes. Neurologic sequelae including hyperactivity, impulsivity, emotional liability, cognitive deficits, and persistent motor deficit could persist long after the acute attacks of cerebellar encephalopathy had resolved.

The first child discussed today illustrates this phenomenon of persistent neurologic dysfunction despite absence of tumor or of opsoclonus/myoclonus. Four of the 10 patients studied by Telander et al. had IQ scores less than 90, and it is interesting to note that the child with the greatest intellectual impairment (IQ 69) had suffered the greatest number of recurrent episodes of ataxia and myo-

clonus [9]. The number of patients in the study was insufficient to establish a correlation between the severity of persistent neurologic sequelae and the number of exacerbations. The authors nonetheless suggest that prompt recognition and treatment of relapses may affect long-term neurologic outcome.

Finally, the symptoms and signs can persist even though the child is completely free of tumor.

Dr. D'Angio. Can we have it both ways? That is, can we accept that patients presenting with this syndrome without identifiable disease must have a small focus of neuroblastoma somewhere; and then based on the same negative evidence, state that the syndrome can persist after the patient has been rendered free of disease?

Dr. Janss. Let me try to explain this seeming contradiction. The symptoms of opsoclonus and myoclonus may be caused by several agents (Table III). If there is no evidence of intoxication, infection, or neuroblastoma, the cause is said to be "idiopathic." Some of these idiopathic cases may be caused by a focus of neural crest tumor so small that it escapes detection. Even though tumor is found within 3 months of onset of ataxia, opsoclonus, and myoclonus in 60% of cases, a delay in detection of the tumor of up to 4 years after onset of symptoms has been reported [9]. It could be argued that patients with exacerbations of cerebellar encephalopathy have an undetectable focus of tumor and the effects of the tumor are enhanced by an additional immunologic burden caused by infection or surgical invasion. However, these children may be symptom-free in intervals between episodes. This pattern is more likely to be the result of the unmasking of an underlying injury caused at the time of tumor presentation, or by increased produciton of immunoglobulins, including those autoantibodies that may be responsible for the symptoms of cerebellar encephalopathy and which are now a part of the child's immunologic memory.

Dr. Sladky. The clinical reports indicate that it would be wise to treat the neurologic disorder immediately and not hope that the opsoclonus/myoclonus will disappear when the primary tumor is brought under control.

Dr. D'Angio. Are there any changes visible at the morphologic level in these children who come to autopsy?

Dr. Sladky. Pathologic studies of the brain in children with neuroblastoma-related opsoclonus/myoclonus syndromes are, by nature, nonsystematic, relatively scarce, and inconsistent. There are one or two references in the literature that describe loss of Purkinje and granule cells in the cerebellum or perivascular cellular infiltrates in the brainstem [11,12]. More widespread pathological changes in cerebrum, brainstem, and spinal cord have been reported in adults with paraneoplastic syndromes that included myoclonus and were associated with other types of malignancies. The short answer is that there are no specific pathological features in the central nervous system for this disorder.

Dr. Janss. In summary, this syndrome in children with neuroblastoma is associated with a low mortality but there may be pervasive and permanent neurologic morbidity. The neurologic findings in the opsoclonus-syndrome point to the brainstem and basal ganglis, respectively, while the other findings of irritability, loss of language skills, and encephalopathy suggest a global central nervous system injury. Residual psychomotor retardation and cognitive and motor dysfunction that persist even after the focal symptoms of opsoclonus and myoclonus have abated support the contention that this syndrome is due to widespread damage. Although the etiology of the syndrome is still unclear, there is some clinical evidence that aggressive treatment of the acute exacerbations of ataxia, opsoclonus, and myoclonus with immunosuppressive therapy may be associated with a better neurological outcome.

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Series Editor's Note

The terms that appear in this Proceedings are straightforward for the most part starting with "ataxia" (Greek: lack of order) and "myoclonus" (Greek: *mys* =

muscle + *klonos* = turmoil). "Opsoclonus," which at first appears to be oxymoronic, is actually very apt (Latin: *aptus* = fastened, from *apisci* = to grasp). It is not derived from the Greek *opson* = dainty, but from *opsis* = vision; therefore, "vision in turmoil." This would seem an accurate description of what these unfortunate patients must experience. *Nystagmus* is less direct, the Greek root *nystazein* meaning "to nod" as from drowsiness.

From Latin roots come two other self-explanatory terms, "conjugate" and "cognitions," the former from *con* = together + *jugare* = to join, from *jugum* = yoke. "Cognition" is from *cognoscere* = to become acquainted with, which is the stem from which William Whewell of Cambridge coined the word "science" in 1840 (according to J.T. Shipley).

"Intelligence" is of Latin origin, too (*intelligere* = to understand), which is clear enough, but how "to stand under" (from Old English roots) came to have this meaning is not obvious. "Overstand" would make some sense, suggesting one is above the material, but that's not what the man said.